# The genus *Gelsemium*: An update

**V. Dutt, S. Thakur[1], V. J. Dhar[2], A. Sharma[3]**

*Guru Gobind Singh College of Pharmacy, Yamuna Nagar, Haryana, [1]S.D. College of Pharmacy, Barnala, [2]Swift School of Pharmacy, Rajpura, Punjab, [3]University Institute of Pharmaceutical Science, Punjab University, Chandigarh, India*

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## ABSTRACT

The review includes 103 references on the genus *Gelsemium*, and comprises ethnopharmacology, morphology, phytoconstituents, pharmacological reports, clinical studies and toxicology of the prominent species of *Gelsemium*. Alkaloids and iridoids constitute major classes of phytoconstituents of the genus. Most popular species of the genus are the Asian G. elegans and the two North American related species, *G. sempervirens* and *G. rankinii*. *Gelsemium* species are categorized under medicinal as well as poisonous plants. Amongst various species, *G. elegans* and *G. sempervirens* possess medicinal value, and have been traditionally used as nervous system relaxant. These plants have been explored exhaustively for their anticancer activity. In the concluding part, the future scope of *Gelsemium* species has been emphasized with a view to establish their multifarious biological activities and mode of actions

**Key words:** Alkaloids, anticancer, *gelsemium*, Iridoids

## INTRODUCTION

The literature review on *Gelsemium* has been compiled using references from major databases such as Chemical Abstracts, Medicinal and Aromatic Plants Abstracts, PubMed, King's American Dispensatory, Raintree Nutrition Incorporation, Henriette's Herbal Homepage, National Agricultural Library (AGRICOLA), Duke's Phytochemical and Ethnobotany database, UK Cropnet Ethnobotany database, Archives of American Folk Medicine and USPTO Patent Full Text and Image database.

The available information on *Gelsemium* has been divided into six sections, that is, ethnopharmacology, morphology, phytoconstituents, pharmacological studies, clinical studies, toxicology, covering prominent species of *Gelsemium*. The ethnopharmacological section has been further subdivided into two sections, that is, traditional uses, and alternative and complementary medicinal uses. The reports, in which *Gelsemium* species have been used as domestic remedy by common men without any prescription for the treatment of various ailments, have been discussed under traditional uses. The subhead 'alternative and complementary medicinal uses' highlights *Gelsemium* species as medicine prescribed by medical practitioners for the treatment of various ailments. It also mentions uses for which *Gelsemium* species or their preparations are available in the market. Under every section, *Gelsemium* species have been arranged in an alphabetical order.

**Address for correspondence:**
Dr. Vandana Dutt,
E-mail: Vandudatt2006@rediffmail.com

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## THE GENUS *GELSEMIUM*

### Taxonomic classification

| | |
|---|---|
| Kingdom | : Plantae (plants) |
| Superkingdom | : Tracheobionta (Vascular plants) |
| Superdivision | : Spermatophyta (Seed plants) |
| Phylum | : Embryophyta (Higher plants) |
| Class | : Magnoliopsida (Dicotyledons) |
| Order | : Gentianales |
| Family | : Loganiaceae |
| Genus | : Gelsemium |
| Species | : elegans, rankinii, sempervirens |

The genus *Gelsemium* belongs to family Loganiaceae, and comprises about five species that are widely distributed throughout Central America. *Gelsemium elegans* known as Lemuan is an extremely poisonous plant that is indigenous to the South East Asian countries and found predominantly in Malaysia and Sarawak.[1-3] Most popular species of the genus are the Asian *G. elegans* and the two North American related species, *G. sempervirens* and *G. rankinii*.[4] *Gelsemium* is a climbing plant with dark evergreen leaves and all parts are poisonous.[5,6]

## ETHNOPHARMOCOLOGY

### Traditional uses

*Gelsemium elegans* has been traditionally used as a nervous system relaxant to treat various types of pain including headache and

pain associated with inflammatory conditions.[5,6] *Gelsemium* is one of homeopathy's important remedy for influenza.[7] *Gelsemium sempervirens* Ait. Syn. *G. nitidum*, commonly known as Yellow jasmine, has been used in the treatment of restlessness, mental irritability, insomnia, headache, irritation of the urinary tract, hyperemia and convulsions.[8] The roots of *G. sempervirens* have been used in the treatment of migraine, neuralgia, rheumatism, and in ovarian and uterine pain.[9] In the US, it has been extensively used as an arterial sedative and febrifuge in various fevers. It has been used in treatment of spasmodic disorders such as asthma and whooping cough. The plant has been used in hysteria, dysmenorrhea, chorea, pneumonia and bronchitis.[10]

### Alternative and complimentary medicinal uses

An herbal preparation containing *G. sempervirens* has been used for evening cold and influenza.[11] Pharmaceutical formulations containing *G. sempervirens* as one of the constituents have been used for the treatment of psoriasis and neurodermatitis[12] Nebera *et al.* reported that homoeopathic preparations, containing *G. sempervirens* in the form of sugar granules, are used in treating myopia of I, II or III degree.[13] Fluid extract of the plant has been used for its spasmolytic actions.[14]

## MORPHOLOGY

*Gelsemium* includes three species of shrubs and climbers from United States and Central America and one species from China, South East Asia and Indo-Malaysia. *Gelsemium elegans* Benth. is a large, woody, evergreen climber with corky bark; leaves ovate or ovate-lanceolate; flowers golden yellow; sepals ovate, margin minutely ciliate; corolla funnel shaped, lobes imbricate in bud; ovules numerous in each cell; style filiform, at the apex with four short stigmatic branches.[15,16] *Gelsemium sempervirens* is a climbing shrub indigenous to the Southern United States from Virginia to Florida and Texas.[17] The plant is supplied commercially as segments of the cylindrical rhizome with attached wiry roots;[18] rhizome horizontal, the segments 3 to 20 cm in length and 3 to 30 mm in diameter, externally moderate brown to dark yellowish-orange, frequently spirally twisted, longitudinally wrinkled, with purplish-brown longitudinal lines and transverse fissures, upper surface with few stem scars, the under and lateral portions with several roots and root scars, fracture of rhizome tough, splintery, internally exhibiting a narrow purplish-brown bark, a broad, pale yellowish orange to light yellow, finely radiate and eccentric wood, a minute disintegrated pith; roots up to 20 cm in length and 2 to 8 mm thick, light brown, nearly smooth and wiry; fracture one-half transverse, the other oblique and splintery, fractured surface showing a broad, radiate, yellow wood and a thin bark.[15]

## PHYTOCONSTITUENTS

A survey of literature reveals that alkaloid constitutes the major class of phytoconstituents in *Gelsemium* species. Table 1 summarizes phytoconstituents reported from various species of *Gelsemium*.

## PHARMACOLOGICAL STUDIES

It has been reported that alkaloidal fraction isolated from *G. elegans* exhibits analgesic and anti-inflammatory activities.[72] A growth stimulant for pig has been prepared from gouwen (*G. elegans*) that served to promote nutrient absorption of organism, to increase immunity, and raise lean-to-fat pork ratio.[73] Cueilleron *et al.* reported that *Gelsemium* tincture at higher concentration inhibits dopamine, noradrenaline and serotonin uptake into synaptosomal preparations from different parts of the rat brain, whereas lower concentrations enhances noradrenaline and serotonin uptake into mesencephale preparation.[74] Methanol extract of *G. elegans* leaves exhibited high cytotoxicity against the human ovarian cancer cell lines CaOV-3 with an IC50 value of 5 μg/ml after 96 h of incubation while less toxicity against the human breast cancer cells MDA-MB-231 suggesting its selectivity towards CaOV-3 cells.[75] Uncarinic acid E, isolated from *G. elegans,* reported to exhibit antitumor effects due to its growth inhibitory activity for HepG2 cells in dose-dependent manner.[76] Gelsedine type alkaloids of *G. elegans* exhibited potent cytotoxic activity in an A431 human epidermoid carcinoma cell line.[52-77] Koumine (50 mmol/L) induced apoptosis of human colon adenocarcinoma LoVo cells in a time-dependent manner, and inhibited DNA synthesis in LoVo cells *in vitro*.[78] Koumine (20–320 μg/ml) dose dependently inhibited concanavalin A or phytohemagglutinin-induced proliferation of murine lymphocytes determined by MTT colorimetry.[79] It also decreased IL-2 level in the cell culture supernatant measured by enzyme-linked immunosorbent assay. Koumine showed remarkable inhibitory effect on mouse vaginal epithelial cell mitosis and promoted the formation of epidermal glandular layer in the scales at the mouse tail.[80] It also decreased serum IL-2 level in mice at concentrations 6, 30, 150 mg/kg. These activities infer that the therapeutic effect of Koumine against psoriasis is related to the inhibition of epidermal cell proliferation, promoting the formation of glandular cells and decreasing the serum level of IL-2. Koumine injection significantly decreased mouse spontaneous activity in moderate and high doses but did not produce any effect on the respiratory and cardiovascular system of dogs.[81]

Low doses of *G. sempervirens* and *Atropa belladonna* showed significant neurotropic and protective effects on behavioral and gastric alterations induced by foot shock stress in mice.[82] Ethanolic extract of *G. sempervirens* has been reported to increase the resistance of rabbits to pneumococcus toxin.[83] *G. sempervirens* alkaloidal fraction possessed anticancer activity as evidenced by significant inhibition of hepatic carcinoma $HepG_2$ cells *in vitro* using crystal violet dyeing method.[84] Sempervirine nitrate, isolated from *G. sempervirens*, exhibited antimitotic activity in mice bearing several types of tumors.[85] Sempervirine has also been reported to possess vasoconstrictor action in the perfused isolated rabbit ear.[86] In an experiment performed by Hinsdale on isolated rat intestine, *G. sempervirens* produced an immediate relaxation of the intestine tissue.[87] *G. sempervirens* and *Datura stramonium* in appropriate concentration reported to prevent development of spontaneous seizures induced in rats by lithium or pilocarpine.[88]

## CLINICAL STUDIES

Gouwen injection, prepared by using alkaloids extracted from *G. elegans* roots, has been reported to exhibit antitumor effect against esophagus cancer in humans.[89] An injection containing *G. sempervirens* extract as one of the ingredients when given to patients suffering from neurodermatitis, resulted in subsidence of itching associated with neurodermatitis after 1 week, disappearance of large erythema after 3–4 weeks and elimination of disease after 6 weeks.[12]

## TOXICOLOGY

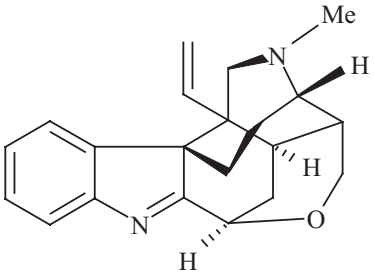
*Gelsemium* acts in the similar manner as nicotine and coniine. Sometimes small doses of *G. sempervirens* can produce toxic symptoms.[9] A drachm of fluid extract of the plant can cause death, and 30 minims are dangerous. An alkaloid gelsemicine from *G. sempervirens* is toxic, and symptoms of toxicity are depressed respiration, tremors, paralysis of extremities, convulsions, urination, defecation, retchings and salivation.[90] Gelsemicine, in small doses, stimulates respiration and paralyzes the respiratory centers in larger doses.[91] The minimum lethal dose is 0.02 to 0.03 mg/g, s.c. for frogs, 0.00010 to 0.00012 mg/g, s.c. for rats, 0.00005 to 0.00006 mg/g, i.v. for rabbits and 0.0005 to 0.001 mg/g, i.v. for dogs. E-Bay website rated extracts of *Gelsemium* 'extremely toxic'.[92] The roots of *G. sempervirens* contain a resin, which is poisonous in very small doses. A tincture prepared by digesting it in undiluted alcohol is fatal. Small doses of *G. sempervirens* relax the muscles but larger doses cause dropping of the lower jaws and difficulty in managing the eyelids. The continued administration of it affects the brain spinal centers and medulla, causing marked feebleness of muscular movements, confusion of vision and vertigo. Large doses paralyze the spinal cord and cause almost complete loss of muscular power. These effects are due to its action upon the spinal marrow. The characteristic toxic symptoms are peripheral relaxation, disturbance of the ocular muscles, drooping of the lower jaw and profound prostration and muscular relaxation. When applied locally to the eye, it dilates the pupils. Overdosage of the plant may cause death due to asphyxia. Alkaloid fraction, isolated from *G. elegans* leaves, at a lethal dose produced violent clonic convulsions that led to respiratory failure. Authors suggested that alkaloids act centrally against GABA as evidenced by prevention of convulsions by pentobarbital or diazepam and potentiation by reserpine.[8]

Persons are reported to have been poisoned by eating honey gathered by the bees from *G. sempervirens* flowers. *Gelsemium* when administered to rabbits and guinea pigs produced a marked generalized congestion of all organs, depressive action on heart and respiration and severe toxic action on liver, kidney and testes.[93] Histological studies showed neurological signs characterized by marked progressive weakness and convulsions culminating in death in three goats over a 24-h period after ingestion of *G. sempervirens* leaves.[94] Aqueous extract of the plant greatly depressed the activity of the isolated frog heart muscles.[95] It has been reported that single intravenous injection of gelsemine (0.2 mg/kg), isolated from *G. sempervirens*, in chloralosed dog produced a marked and prolonged decrease in blood pressure.[96] Alkaloids gelsemine, sempervirine and gelsemicine, isolated from *G. sempervirens*, increased the hypertensive action of adrenaline[91] and inhibited the cholinesterases of nervous tissue and serum.[97] The drug is used as poison as it effects vary rapidly.[98,99]

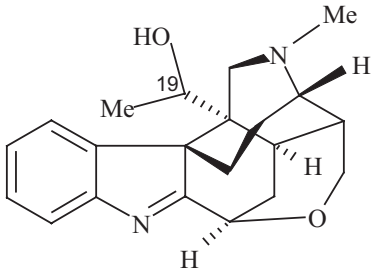
**Table 1: Phytoconstituents of various species of Gelsemium**

| Species | Phytoconstituents |
|---|---|
| *G. elegans* | Alkaloids koumine,[1] kounidine, kouminine, kouminidine, koumicine, kouminicine,[19-28] 19-(R)-and 19-(S)-hydroxydihydrokoumine,[2,3,29] 19-(R)- and 9-(S)-kouminol[4,5,30] humantenine,[6] 11-hydroxyhumantenine,[7] 15-hydroxyhumantenine, 11-methoxy-humantenine,[8] N-desmethoxyhumantenine,[9] rankinidine,[10] 11-hydroxyrankinidine,[11] N-desmethoxy-rankinidine,[12] 20-hydroxydihydrorankinidine, humantenirine,[13] humantendine,[14] gelsemoxonine,[15,31-36] gelsamydine,[37] 19 α-hydroxygelsamydine,[16] 14 α-hydroxygelsamydine,[17] 14 -hydroxyelegansamine,[18] Gelsebanine,[19,38,39] koumidine,[20] 19-(Z)-akuaminidine,[21] 16-epi-voacarpine,[22] 19-hydroxy-dihydrogelsevirine (40), gelsemine,[20-22,23] gelsevirine,[24] 19-(R)-acetyldihydrogelsevirine, 19-(R)-hydroxydihydrogelsemine,[41] gelsemicine,[25] gelsedine,[26,42] elegansamine,[27,43] N-methoxy-anhydrovobasinediol,[28,44] gelsemamide,[29] 11-methoxygelsemamide,[45] 11-methoxy-19-(R)-hydroxygelselegine,[29,30] sempervirine,[46-50] Gelsedilam,[31] 14-acetoxygelsedilam,[32] gelsefuranidine,[33] gelseinidone,[34,51] 14 acetoxygelsenicine,[35] 14 acetoxy-15-hydroxygelsenicine,[36] 14-acetoxy-19-oxogelsenicine,[37] 14-acetoxygelselegine;[38,52] humantenine N(4)-oxide.[100] Iridoids (53) gelsemide,[39] GEIR-1,[40] GRIR-1,[41] GEIR-2,[42] GEIR-3,[43] Di(2-ethylhexyl) phthalate, 3β-hydroxyl-27-p-(Z)-coumaroyloxy ursan-12-en-28-oic acid, 3β-hydroxyl-27-p-(E) coumaroyloxy ursan-12-en-28-oic acid, uncarinic acid (Wei et al., 2007), β-sitostreol, stigmasterol, daucosterol, stigmasterol, β-D-glucopyranoside, ursolic acid, gallic acid, ferullic acid, protocate chulic acid.[101] Glycosides; Gelsemiunoside A and B.[102] |
| *G. rankini Small* | Alkaloids 21-oxogelsevirine, 21-oxogelsimine, gelsivirine,[24] gelsemine,[24,54] rankinidine,[10] humantenirine,[14] humantenine;[6,55] Iridoids gelsemide,[39] GEIR-1,[40] GRIR-1,[41] GEIR-2,[42] GEIR-3.[43,53] |
| *G. sempervirens* | Alkaloids gelsemine,[23] gelseminine, gelsemoidine, gelsemicine,[25,56-62] 21-oxogelsemine,[63] gelsevirine,[24,64] gelsedine,[24,48] 14-hydroxygelsemicine,[65,66] 14β-hydroxygelsedine,[67,68] sempervirine,[46,47,60] gelsedine type oxindole alkaloids,[69] gelsemic acid;[70] Iridoids gelsemide,[39] gelsemide-7-glucoside, gelsemiol,[44] gelsemiol 1- and 3-glucoside, 9-hydroxysemperoside;[71] 2008 Steroids pregna-4,16-diene-3,20-dione, 12 β-hydroxy-5α-pregna-16-ene-3,20-dione, 12 β-hydroxypregna-4, 16-diene-3,20-dione,[68] Scopoletin,7-O-beta-D-glucopyranosylscopoletin,7-O-beta-D-apiofuranosyl-(1->6) β-lucopyranosylscopoletin,Uvaol,2-(4-hydroxyphenyl) ethylheptadecanoate.[103] |

## APPENDIX

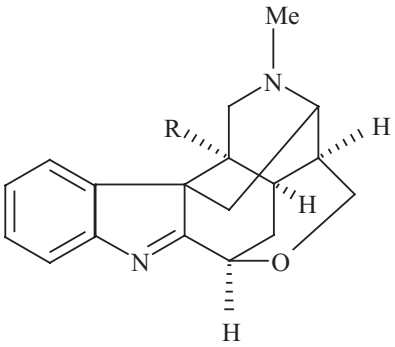


**1**

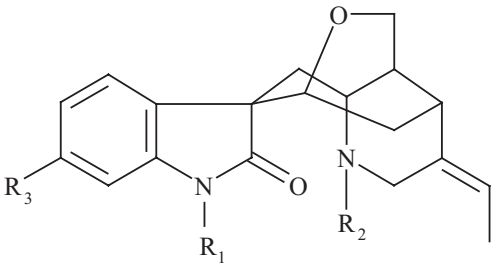


**2** 19-(R)

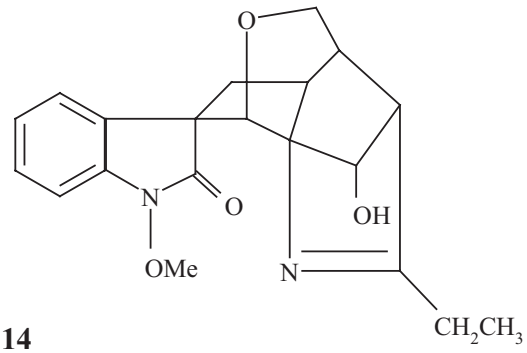
**3** 19-(S)



| R | |
|---|---|
| **4** | $CHOHCH_3$ (R) |
| **5** | $CHOHCH_3$ (S) |



| | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| **6** | $OCH_3$ | $CH_3$ | H |
| **7** | $OCH_3$ | $CH_3$ | OH |
| **8** | $OCH_3$ | $CH_3$ | $OCH_3$ |
| **9** | H | $CH_3$ | H |
| **10** | $OCH_3$ | H | H |
| **11** | $OCH_3$ | H | OH |
| **12** | H | H | H |
| **13** | $OCH_3$ | H | $OCH_3$ |



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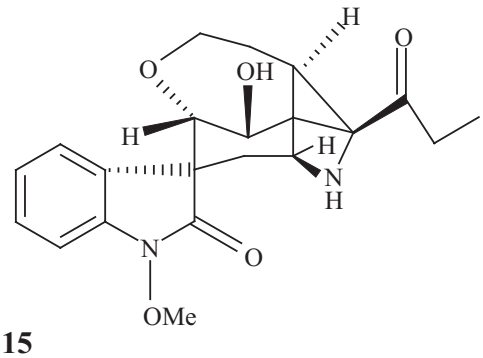

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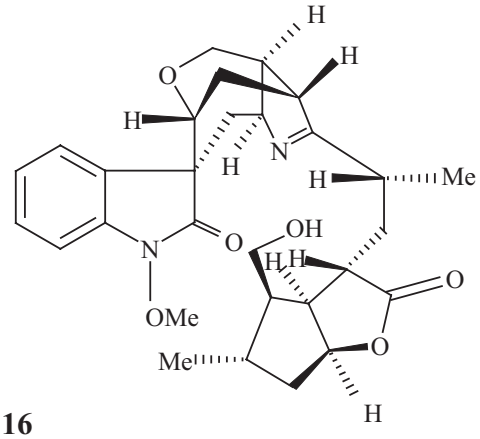

**16**

*Appendix (contd...)*

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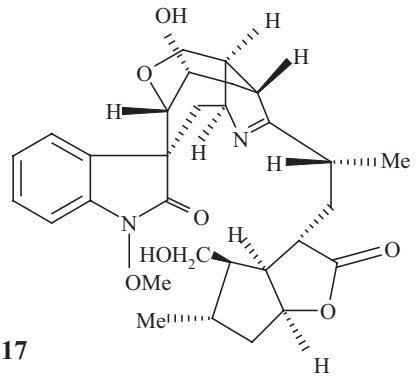

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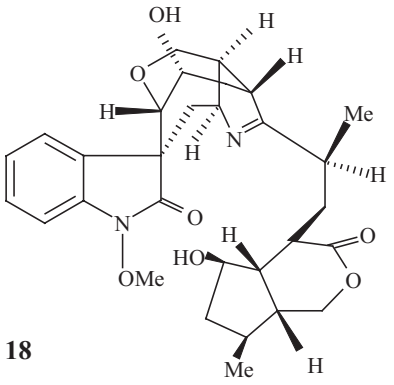

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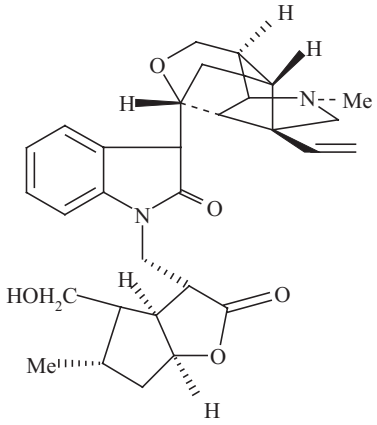

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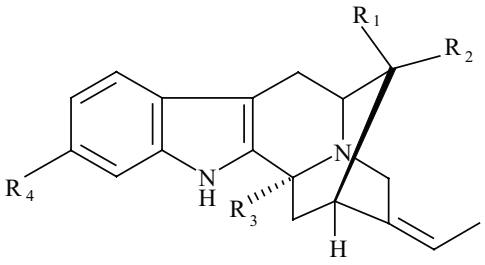
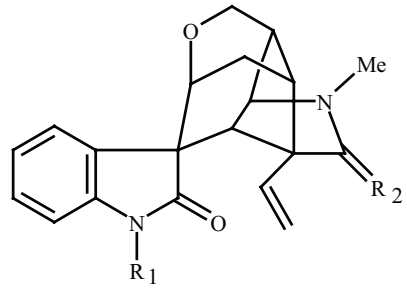
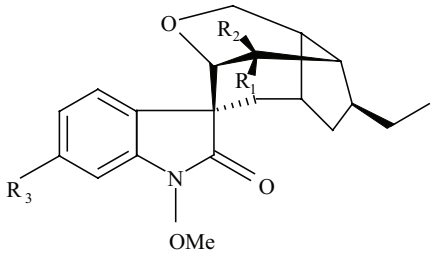


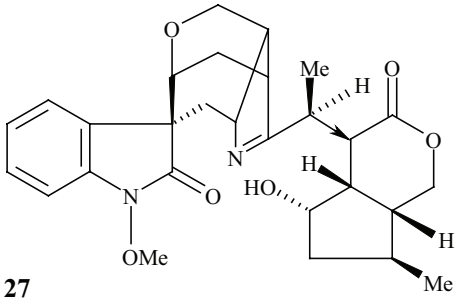
| | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|
| **20** | $CH_2OH$ | H | H | H |
| **21** | $CO_2CH_3$ | $CH_2OH$ | H | H |
| **22** | $CH_2OH$ | $CO_2CH_3$ | OH | H |



| | $R_1$ | $R_2$ |
|---|---|---|
| **23** | H | $H_2$ |
| **24** | $OCH_3$ | $H_2$ |



| | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| **25** | H | H | $OCH_3$ |
| **26** | H | H | H |



**27**

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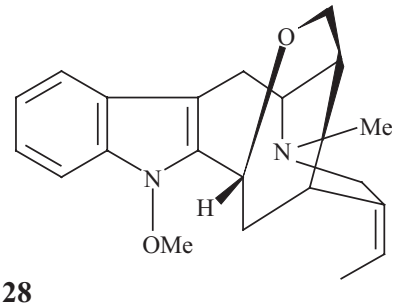

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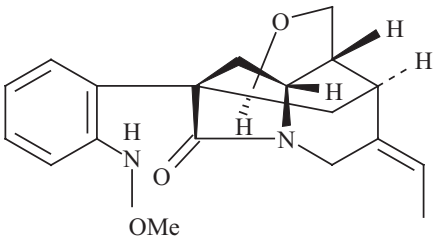

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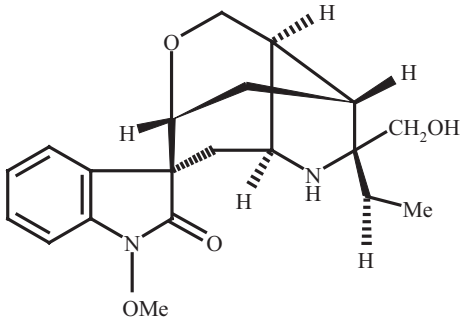

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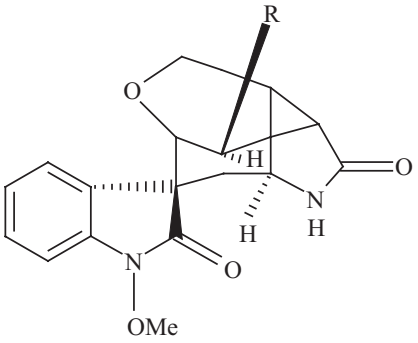
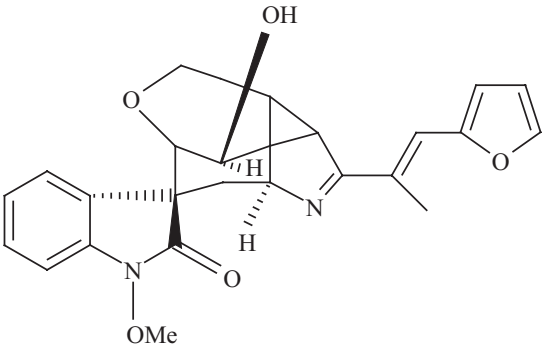
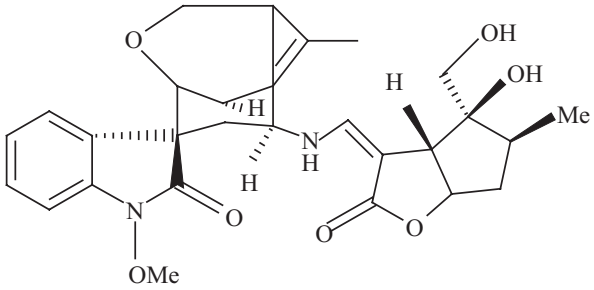


**31** R = H

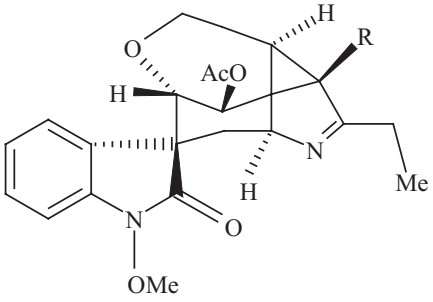
**32** R = OAc



**33**

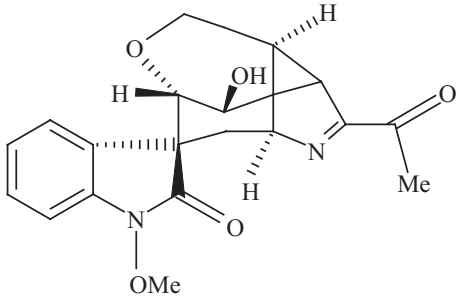


**34**



**35** R = H

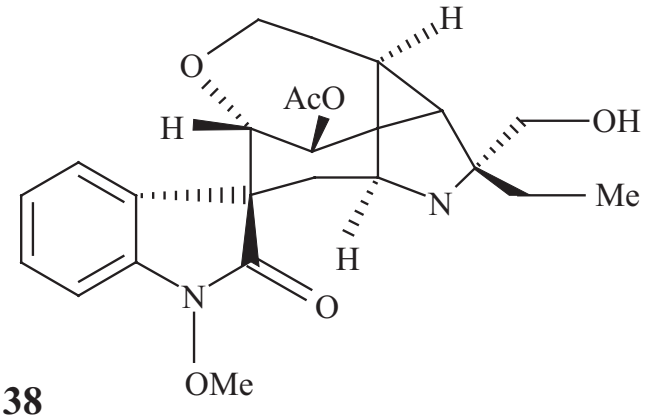
**36** R = OH



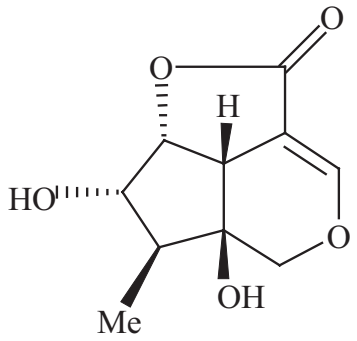
**37**

*Appendix (contd...)*

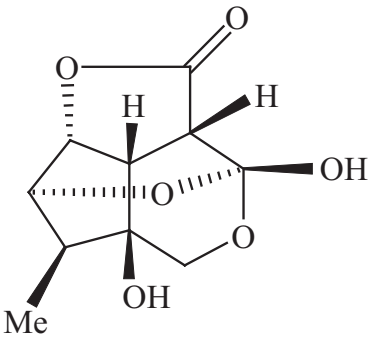
*Appendix (contd...)*



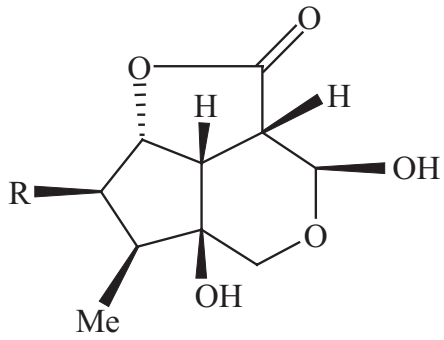

**38**




**39**



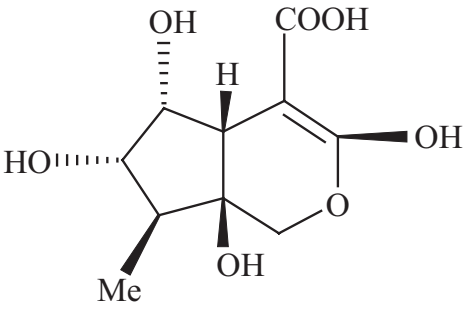

**40**



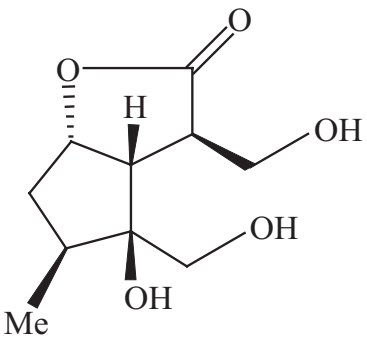

**41** R = OH

**42** R = H

**43**




**43**




**44**

## CONCLUSION

About 05 species of the genus *Gelsemium* have been reported in various floras. An exhaustive survey of literature revealed that information is available on 03 species. Among these 05 species, most of ethnopharmacological reports are available on *G. elegans and G. sempervirens*. Further, these plants [Table 1] have been investigated for their phytoconstituents.

*Gelsemium sempervirens* has been included in a number of herbal and homoeopathic formulations, which are in clinical use for the treatment of various ailments. Mother tinctures of the

plant are available in Indian market, and are frequently used for the treatment of CNS disorders, but no pharmacological work supports its efficacy in CNS disorders. Keeping in view the traditional, alternative and complimentary medicinal uses, and frequency of use in homoeopathic formulations, *G. sempervirens* seems to hold great potential for in-depth investigation on various biological activities, especially its effect on the central nervous systems.

A close scrutiny of literature on *Gelsemium* reveals that two species have been investigated pharmacologically. Pharmacological studies infer that *G. elegans* exhibits analgesic, antiinflammatory and cytotoxic properties; *G. sempervirens* exhibits neurotropic and antitumor activities. Koumine, gelsedine type alkaloids and uncarinic acid E have been considered bioactive constituents of *G. elegans*. Toxicological studies have confirmed high toxicity of *Gelsemium* species at higher doses. These plants have narrow therapeutic index, that is, margin between therapeutic efficacy and toxic value is very less. Although the plants of the genus *Gelsemium* hold great potential to be developed as antitumor drugs, their toxicity could not be ruled out.

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